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PATENT
Our Docket: P-LA 1245

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:
Border and Ruoslahti

Serial No.: 08/349,479

Filed: December 2, 1994

For: INHIBITING TRANSFORMING GROWTH FACTOR β TO PREVENT ACCUMULATION OF EXTRACELLULAR MATRIX

Group Art Unit: 1644

Examiner: P. Gambel

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231, on August 2, 2002.

By Astrid R. Spain
Astrid R. Spain, Reg. No. 47,996

August 2, 2002
Date of Signature

Commissioner for Patents
Washington, D.C. 20231

REPLY BRIEF PURSUANT TO 37 C.F.R. §1.193(b)

Sir:

Responsive to the Examiner's Answer mailed June 4, 2002, consideration of the following remarks respectfully is requested.

REMARKS

A single issue is the subject of the present appeal:

1. Whether Appellants' Declaration under 37 C.F.R. § 1.131, filed on March 15, 2001, is sufficient to antedate U.S. Patent No 5,772,998 to Dasch et al.

Regarding the Issue on Appeal

The Examiner's Answer takes issue with Appellants' position that the after-final amendment splitting Markush-type claim 23 into two separate claims, amended claim 23 and new claim

35, each directed to a single species, does not raise new issues by introducing new claim elements or limitations.

Briefly, concurrently with the filing of their Appeal Brief, Appellants filed a Supplemental Response with proposed claim amendments. The pending claims and the claims showing the proposed after-final amendment were attached as Appendices A and B, respectively, to Appellants' Appeal Briefs of October 15, 2001 and February 27, 2002. If entered, Appellants' proposed claim amendments would have resulted in splitting Markush-type claim 23 into two separate claims, amended claim 23 and new claim 35, each directed to a single species.

On February 2, 2002, the Examiner issued an Advisory Action and Notice of Non-Compliance with 37 C.F.R. § 1.192(c), both of which asserted that Appellants' after-final amendment was improperly used as a basis for new issues argued in Appellants' Appeal Brief rendering the Brief defective under Rule 192(c). In a subsequent telephonic interview with the Examiner on February 26, 2002, Appellants' representative argued and the Examiner agreed that the only issue addressed in the Appeal Brief of October 15, 2001, is priority of invention as set forth in section VI of the Brief. The Examiner further conceded that the Appeal Brief of October 15, 2001, was not defective under Rule 192(c). An Interview Summary of the February 26, 2002, telephonic interview was previously attached as Appendix E to Appellants' Appeal Brief of February 27, 2002.

As set forth above, the sole basis for holding Appellants initial Appeal Brief defective was the allegation that new issues were raised by splitting the Markush-type claim. The Examiner then reversed his position and conceded that the Appeal Brief was not defective, in other words, that no new issues were raised and priority remained the sole issue on appeal. In the Examiner's Answer, it is now again argued that the splitting up of Markush-type claim 23 into two separate claims, amended claim 23 and new claim 35, each directed to a single species, does raise new issues by introducing new claim elements or limitations.

Appellants maintain that the only issue on appeal is whether Appellants' Declaration under 37 C.F.R. § 1.131, filed on March 15, 2001, is sufficient to antedate U.S. Patent No 5,772,998 to Dasch et al. Contrary to the Examiner's assertion, no new issues are raised by the splitting of the Markush-type claim 23 into two separate claims. Appellants respectfully submit that a distinction exists between new issues and further arguments with regard to the same issue. While priority remains the sole issue on appeal, splitting Markush-type claim 23 into two separate claims, each directed to a single species, merely puts the claims in better form for consideration on appeal with regard to examination of the priority issue. Consequently, Appellants respectfully submit that the amendment splitting Markush-type claim 23 into two separate claims makes the final amendment proper based on 37 CFR 1.116(a):

> After a final rejection or other final action (1.113), amendments may be made cancelling claims or complying with any requirement of form expressly set forth in a previous Office action. Amendments presenting rejected claims in better form for consideration on appeal may be admitted. The admission of, or refusal to admit, any amendment after final rejection, and any related proceedings, will not operate to relieve the application or patent under reexamination from its condition as subject to appeal or to save the application from abandonment under 1.135.

In view of the above, Appellants respectfully request that the Board consider the claims set forth in Appendix B of the Appeal Brief.

Regarding the Grouping of Claims

The Examiner's Answer takes issue with Appellants' argument that the claims do not stand or fall together.

37 C.F.R. § 1.192 (c)(7) allows an appellant to take a position in the appeal brief on whether or not the appealed claims stand or fall together:

> (c) The brief **shall** contain the following items under appropriate headings and in the order indicated below unless the brief is filed by

> an applicant who is not represented by a registered practitioner:
> ...
> (7) Grouping of claims. For each ground of rejection which appellant contests and which applies to a group of two or more claims, the Board shall select a single claim from the group and shall decide the appeal as to the ground of rejection on the basis of that claim alone unless a statement is included that the claims of the group do not stand or fall together and, in the argument under paragraph (c)(8) of this section, appellant explains why the claims of the group are believed to be separately patentable. Merely pointing out differences in what the claims cover is not an argument as to why the claims are separately patentable.

Appellants maintain that the claims do not stand or fall together for the reasons set forth throughout Appellant's Brief and summarized in the paragraph spanning pages 17 and 18:

In order to antedate a reference that has been cited against an application, distinct requirements exist that depend, in part, on whether the application claims a genus or species and, in part, on the species disclosed in the cited references. Consequently, claims 21-23 and 25 must be separately examined with regard to whether Appellants have made the necessary showing for prior invention of the claimed subject matter. It is for that reason, claim 21, directed to a genus, and claims 22, 23, 25 and, if

entered, claim 35, each directed to distinct species, do not stand and fall together.

Appellants respectfully submit that, in their Appeal Brief, Appellants were entitled to take a position with regard to whether the claims stand or fall together. Since during regular prosecution all pending claims are under examination, it is not necessary for an applicant to take a position with regard to whether or not the claims stand or fall together, nor is there a requirement under either federal case law or statutory law to take a position in this regard.

In sum, Appellants were entitled to argue in their Appeal Brief that the claims are separately patentable and respectfully maintain that claim 21, directed to a genus, and claims 22, 23, 25 and, if entered, claim 35, each directed to distinct species, do not stand and fall together for the reasons set forth in the Appeal Brief.

Regarding Sufficiency of the 37 C.F.R. § 1.131 Declaration

Claim 21 is a genus claim directed to a method of decreasing the deleterious accumulation of extracellular matrix (ECM) associated with a pathology or a condition characterized by the TGF-β-induced production and deleterious accumulation of extracellular matrix in a tissue, while claims 23, 25 and, if entered, new claim 35, are species claims that recite the

specific pathologies adult respiratory distress syndrome, liver cirrhosis and scarring.

The Dasch et al. '998 patent describes a method of neutralizing the inhibitory effects of TGF-β and further references several species of pathologies, including interstitial lung fibrosis, liver cirrhosis, fibrotic skin disorders such as scleroderma and scarring. In Appellants' Declaration pursuant to 37 C.F.R. § 1.131 submitted on March 15, 2001, Drs. Border and Ruoslahti aver that they conceived, prior to December 22, 1988, the claimed methods of decreasing the TGF-β-induced production and deleterious accumulation of extracellular matrix associated with a pathology or a condition, including glomerulonephritis, adult respiratory distress syndrome, cirrhosis of the liver, and scarring, by contacting the affected tissue with an anti-TGF-β antibody. Appellants' Rule 131 Declaration of March 15, 2001, is further supported by corroborating Exhibits A through E, which were specifically and individually addressed in Appellants' Brief and which corroborate various elements of the claimed invention. Viewed in context, Appellants' Declaration and accompanying Exhibits A through E, serve to establish Appellants' conception of the claimed methods prior to December 22, 1988, as well as Appellants' diligence in the pursuit of reducing to practice the claimed methods from prior to December 22, 1988, until the filing of the priority application. Appellants' Rule 131 Declaration of March 15, 2001, and corroborating Exhibits A through E were attached as Appendix C to Appellants' Appeal Briefs filed October 15, 2001 and February 27, 2002.

Appellants' averments set forth in their Rule 131 declaration are entirely appropriate to establish conception of some of the invention features prior to the effective date of the reference. Directly on point, Ex Parte Ovshinsky, 10 USPQ2d 1075 (Bd. Pat. App. & Inter. 1989) indicates at page 1077:

> We point out to the Examiner that (1) all the evidence must be considered in its entirety, including the Rule 131 declarations and accompanying exhibits, records and 'notes,' (2) **an accompanying exhibit need not support all of the claimed limitations but rather a missing feature may be supplied by the Declaration itself,** and (3) it is entirely appropriate for appellants to rely on a showing of facts set forth in the Rule 131 declarations themselves to establish conception of the invention prior to the effective date of the reference. [Citation Omitted][Emphasis Added]

Appellants maintain that no court has held that in order to show conception prior to a critical date, an applicant has to provide one or more exhibits that explicitly or implicitly contain all elements of the claimed invention. Rather, under the controlling legal standard articulated by the Ovshinsky Court "it is entirely appropriate for appellants to rely on a showing of facts set forth in the Rule 131 declarations themselves to establish conception of the invention prior to the effective date of the reference." However, Appellants' Rule 131 Declaration was supported by Exhibits A through E, each of which corroborates

Appellants' averments either with regard to the conception of the claimed methods prior to December 22, 1988, or Appellants' due diligence in pursuing reduction to practice of the claimed methods during the critical period. Although it does not constitute binding authority, the MPEP is consistent with the case law in stating that evidence in the form of exhibits may accompany the declaration, but does not require such extrinsic evidence (see MPEP §715.07).

The corroborative value of the Declaration under Rule 132 by Lucia Languino, Ph.D., which was submitted as Exhibit A to Appellants' Rule 131 Declaration appears to be discounted at page 7, paragraph 2, of the Examiner's Answer:

Other than the Rule 131 and 132 Declarations, neither Appellant nor Languino have provided any corroborating factual evidence to support the 'stated goals'... .

Appellants respectfully submit that Dr. Languino, who presently is an Associate Professor at Yale University School of Medicine, through her independent third party Declaration, provides independent corroboration of Appellants' averments. In particular, Dr. Languino avers that during her postdoctoral fellowship in Dr. Ruoslahti's laboratory, she was asked to assist in the preparation of anti-TGF-β antibodies for a stated goal of using anti-TGF-β antibodies to inhibit TGF-β in order to decrease the deleterious TGF-β-induced production and accumulation of extracellular matrix (ECM) associated with a disease, including kidney disease. Furthermore, Dr. Languino's

Declaration itself is accompanied by a corroborating exhibit, in particular, a La Jolla Cancer Research Foundation "Animal Usage Form," the redacted date of which is prior to December 22, 1988, related to the project entitled "Anti-human TGF-β Cyclic Peptide," which lists Appellant Dr. Border and Dr. Languino as the investigators. Appellants maintain that Dr. Languino's Rule 132 Declaration provides independent third party corroboration by Dr. Languino of the facts averred to by Appellants in their Rule 131 Declaration.

With regard to Exhibit B to Appellants' Rule 131 Declaration, which consists of two laboratory notebook pages from Dr. Languino's notebook that show the protocol for development of a rabbit anti-TGF-β antiserum and a La Jolla Cancer Research Foundation "Animal Procedure Request" form that indicates the dates on which the animals were bled for anti-TGF-β serum, December 13, 16 and 21 of 1988, the Examiner's Answer indicates at page 7, paragraph 5:

It is noted that the priority date of Dasch et al. is December 22, 1988, which is one day after the final bleeding of the rabbits in the protocol for developing rabbit anti-TGF-β antiserum. Therefore, it appears that the rabbit anti-TGF-β antiserum was not tested prior to the effective priority date of Dasch et al. (U.S. Patent No. 5,772,998).

Appellants respectfully submit that the bleeding schedule of the rabbits is consistent with Appellants' conception of the claimed invention prior to the effective priority date of the Dasch '998

patent. Conception is the formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is to be applied in practice. Hybritech Inc. v. Monoclonal Antibodies Inc., 802 F. 2d 1367, 1376, 231 USPQ 81, 87 (Fed. Cir. 1986). Furthermore, Appellants respectfully submit that testing of the antibodies is not a prerequisite for conception. See Burroughs Wellcome Co. v. Barr Labs., Inc., 40 F.3d 1223, 1228, 32 USPQ2d 1915, 1919 (Fed. Cir. 1994). In this regard, Exhibit C to the Rule 131 Declaration, a conference abstract by Drs. Border and Ruoslahti published for the Meeting of the American Society of Nephrology in San Antonio, Texas, which was submitted prior to December of 1988, entitled "Transforming Growth Factor β (TGFβ) Uniquely Regulates Production of Glomerular Extracellular Matrix" shows Appellants' discovery that TGF-β is unique among growth factors in its ability to stimulate ECM production, which is increased in a variety of pathologies. Based on this discovery, Appellants' conception of using antibodies to inhibit TGF-β in order to decrease the deleterious TGF-β-induced production and accumulation of extracellular matrix (ECM) associated with a disease prior to the effective priority date of December 22, 1988, is consistent with the evidence.

Another specific allegation set forth at page 7, final paragraph, of the Examiner's Answer is that

Appellant asserts without evidence that based upon an in vitro experimental study disclosing the unique role of TGF-β in kidney cell culture, the ordinary artisan would have extrapolated this

finding to reducing extracellular matrix in a wide variety of distinct diseases with TGFβ-specific antibodies.

Appellants respectfully submit that, upon discovering that TGF-β is unique among growth factors in its ability to stimulate ECM production, they conceived the claimed methods of decreasing the TGF-β-induced production and deleterious accumulation of extracellular matrix associated with a pathology or a condition, including glomerulonephritis, adult respiratory distress syndrome, cirrhosis of the liver, and scarring, by contacting the affected tissue with an anti-TGF-β antibody. In other words, Appellants recognized the applicability of the invention method of decreasing the TGF-β-induced production and deleterious accumulation of extracellular matrix to a variety of pathologies associated with extracellular matrix accumulation. In this regard, Appellants note that the Examiner, in rejecting Appellants' pending claims under 35 U.S.C. §103(a) as allegedly rendered obvious by Dasch et al., in view of Ruoslahti et al. (U.S. Patent 5,583,103) and/or Bassols et al., J. Biol. Chem., 263:3039-3045 (1988), argues at page 5, paragraph 2, of the Answer that

one of ordinary skill in the art at the time the invention was made would have been motivated to apply such TGF-β-specific antibodies in other disorders where TGF-β played a role such as glomerulonephritis, as taught by Ruoslahti et al. and Bassols et al.

Thus, the Examiner's Answer effectively argues that the person of ordinary skill at the time of the invention would have been motivated to apply TGF-β-specific antibodies in other disorders, while simultaneously taking the position that it is not reasonable that Appellants, upon discovering that TGF-β is unique among growth factors in its ability to stimulate ECM production, conceived the claimed methods of decreasing the TGF-β-induced production and deleterious accumulation of extracellular matrix associated with a variety of pathologies associated with ECM accumulation. Appellants respectfully submit that it is consistent with the evidence and Applellants' Rule 131 Declaration that, upon discovering that TGF-β is unique among growth factors in its ability to stimulate ECM production, Appellants conceived the claimed methods of decreasing the TGF-β-induced production and deleterious accumulation of extracellular matrix associated with a variety of pathologies associated with ECM accumulation.

Finally, the Examiner's Answer at page 11, paragraph 6, reiterates that

A general allegation that the invention was completed prior to the date of the reference is not sufficient.

To reiterate and summarize, Appellants have provided a Rule 131 Declaration and accompanying Exhibits A through E. The Rule 131 Declaration contains specific averments, not a general allegation that the invention was completed prior to the date of the reference. The Exhibits include a corroborating Declaration

by an independent third party, excerpts form laboratory notebooks, a conference abstract and a manuscript of a grant proposal. Appellants have been held to a standard that cannot be met and that seems to require documentary evidence with regard to each claim feature. Such a standard is not supported in either federal case law or statutory law. In their Appeal Brief, Appellants clearly laid out the controlling legal authority with regard to each claim and addressed every piece of corroborating evidence and, further, explained how each piece of corroborating evidence supports the Rule 131 Declaration.

Appellants respectfully submit that the Rule 131 Declaration of March 15, 2001, and accompanying Exhibits A through E, establish Appellants' conception of the claimed methods prior to December 22, 1988, as well as Appellants' diligence in the pursuit of reducing to practice the claimed methods from prior to December 22, 1988, until the filing of the priority application.

CONCLUSION

In view of the above arguments, Appellants respectfully submit that the Declaration under 37 C.F.R. § 1.131, filed on March 15, 2001, is sufficient to antedate U.S. Patent No. 5,772,998 to Dasch et al. and respectfully submit that the decision of the Examiner, finally rejecting claims 21-23 and 25, should be reversed.

Respectfully submitted,

August 2, 2002
Date

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